

REMARKS/ARGUMENTS

Application Status

Claims 1-6 and 8-20 are pending in the subject application. Claim 7 has been cancelled. Objections to Claims 5, 7 and 20 were withdrawn. Rejection of Claims 1, 8-9 and 13-19, under 35 U.S.C. § 102, were withdrawn. Rejection of claims 1, 8-9 and 13-19, under 35 U.S.C. § 102 were withdrawn.

Rejections Under U.S.C. §103

Claims 1 and 14-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WIPO document No.: 99/10535 to Liu, filed 21 August 1997, published 4 March 1999.

Applicants respectfully traverse.

The Examiner alleges that "Liu '535 obviates all of the limitations of Applicants' claims." (See Office Action, page 3, 3rd paragraph). The Examiner asserts that:

Liu '535 discloses "methods to identify a therapeutic agent that modulates the expression of at least one stem cell gene associated with the differentiation ... of stem cells" (Liu '535 ABSTRACT). Liu teaches the identification of stem cell genes that are differentially expressed at various stages of differentiation by preparing gene expression profiles before and after differentiation (*Id.*, p. 5, lines 1-6).

Based on these allegations, the Examiner asserts that "this encompasses defining those genes that are expressed in a tissue-specific manner, as well as those genes that are down-regulated in a tissue-specific manner and therefore defines the markers that would be analyzed for increased tissue-specific gene expression in step (E) of Claim 1." (See Office Action, page 3, last line through to page 4, 1st paragraph). Applicants respectfully traverse.

Applicants invention, is directed in part to agent-induced gene changes of stem cells and not solely to differentiation of genes that "are expressed in a tissue-specific manner." The cells are analyzed , in step (E) of claim 1 "for increased tissue-specific gene expression" (page 2, lines 6-7 of the instant application) "if an agent that promoted tissue-specific differentiation was in

contact with the stem cells." (See, for example page 2, lines 5-6). In addition, stem cells disclosed by applicants include totipotent stem cells. Applicants disclose that totipotent stem cells are "capable of giving rise to all types of differentiated cells found in the organism from which it is derived." (See, for example page 3, lines 7-8. Emphasis added). Therefore, stem cells disclosed by applicants are not committed to, nor predisposed to, any specific cell lineage.

Regarding the steps disclosed by applicants in claim 1, applicants teach the steps of culturing of embryonic stem cells (*i.e.*, totipotent stem cells) followed by sub-culturing of the stem cells prior to the addition of any agent. Thus, applicants do not merely isolate stem cells and culture "cells *in vitro* in the presence of each substance" as alleged by the Examiner on page 4, 2nd paragraph of the instant Office Action.

In contrast to applicants' invention, Liu '535 does not teach the steps of culturing and sub-culturing of a stem cell, including totipotent embryonic stem cells. Liu '535 is directed to lineage committed stem cells, *i.e.* hematopoietic stem cells, and the identification of genes expressed by these pre-committed stem cells. That is Liu '535 does not teach or disclose identification of any markers in stem cells that have not been committed to a specific cell lineage nor does Liu teach or suggest how to culture and sub-culture stem cells which are not pre-disposed to a specific cell lineage. It is unknown from the reading of Liu whether any totipotent stem cell could even be manipulated to differentiate from a totipotent stem cell to a pluripotent stem cell to a pre-committed stem cell, such as a hematopoietic stem cell.

Regarding the Examiner's allegations that "in view of Liu, one of ordinary skill in the art at the time of invention by Applicant ... would have been motivated to identify drug candidates for promoting tissue-specific differentiation of a stem cell by providing a number of test substances (otherwise there would be no pool of substances from which to identify a substance that works), and culturing cells *in vitro* in the presence of each substance, individually, under conditions that allow for such differentiation, and analyzing the cells in cultures for increased tissue-specific gene expression markers." Applicants respectfully traverse.

Applicants' claim 1 is directed in part to "at least a first test substance and a second test substance, the first and second test substances having different molecular structures." These

first and second test substances with different molecular structures are then administered to stem cells that are first sub-cultured, as discussed above, **before** each sub-culture is exposed to the first and second test substances of different molecular structures.

In contrast, the experiments described in Liu that were actually carried out were limited to generating gene expression profiles from isolated hematopoietic stem cells from 6-12 week old mice. These experiments did not include the performance of even a single step of independent claim 1. Specifically the experiments did not include a step of providing a library of test substances (claim 1, step A), providing an *in vitro* culture of stem cells (claim 1, step B), contacting subcultures of the culture with a test substance from the library (claim 1, step C), culturing the subcultures under conditions that would promote tissue specific differentiation of the stem cells if an agent that promoted tissue specific differentiation was in contact with the stem cells (claim 1, step D), or analyzing the cells in the subcultures for increased tissue specific gene expression (claim 1, step E).

Accordingly, Liu '535 teaches **away** from the methods disclosed by applicants. The Office Action allegation appears to extrapolate well beyond the disclosure of Liu '535, especially when Liu '535 states that stem cells have to be **at different stages** of differentiation and one test substance is used for comparison per stage. Furthermore, Liu '535 does not provide any parameters to define a "defined stage of differentiation" (See, Liu '535 page 17, lines 6-10) especially when Liu '535 is disclosing stem cells of hematopoietic differentiation, *i.e.*, a pre-committed stem cell (See, for example, Liu '535, page 4, lines 23-28; and throughout specification).

Liu '535 would not provide an Artisan with any motivation and/or any expectation of reasonable success to arrive at applicants' teachings. In fact, Liu '535 would be an obstacle to an Artisan to arrive at such teachings in the absence of applicants invention. The methods of the present specification and Liu are different from one another in several respects in addition to the *in vitro* culturing step discussed above. For example, to analyze gene expression, Liu used the method of differential display involving three different gene profiles. Differential display is a laborious and time-consuming method that analyzes a vast number of genes. This technique is

not suited for a high-throughput analysis of a large number of samples. In contrast, the method of the present specification typically involves a PCR-based approach for analyzing cell populations (e.g., two cell populations *vs.* three expression profiles of Liu) for a finite number of genes and is suitable for high-throughput analyses. The method of the present specification is therefore simpler, quicker, and less expensive to perform than the method of Liu.

Furthermore, the Examiner admits that "Liu does not teach the aspects of culturing cells " (see page 7, 1st paragraph of the Office Action). Liu 535', does not, therefore, teach every element of Applicant's claims and the rejection is properly withdrawn. In this regard, attention is directed to Section 2131 of the Manual of Patent Examining Procedure, which states in part:

A claim is anticipated only if and each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Brothers. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the .. claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

The Examiner alleges that "[i]n view of Liu and Moore, it would have been obvious to modify the teachings of Liu by culturing cells in microtiter plates, at 37 degrees centigrade, with 7.5% carbon dioxide, and for 3 to 21 days, as taught by Moore." Applicants respectfully traverse.

As the Examiner has pointed out, "Moore teaches culture media for establishing growing and maintaining mammalian cells in culture." However, Moore is deficient as it does not teach or disclose how to culture and maintain stem cells. Cells disclosed by Moore are malignant and normal cells. (See Example 2). As one of ordinary skill in the art is aware, cells of different types require different media and growth conditions, such as culturing time frames. Moore provides absolutely no guidance as to the culturing and maintenance of stem cells and cannot make up for the deficiencies of Liu, as extrapolated by the Examiner. Accordingly, Liu, in view of Moore, would not provide a reasonable expectation of success and nor would a person of ordinary skill in the art be motivated to combine these two references.

Indeed such motivation can only be provided by an application of the teachings of the instant invention, and such is improper as it constitutes a hindsight reconstruction of Applicants' invention. Moreover, assuming, *arguendo*, such a motivation existed, one of ordinary skill in the art still would have no expectation of success, as neither of these two references teach the culturing of stem cells.

It is respectfully submitted that for the foregoing reasons, claims 1 and 14-19 are patentable over the cited references and satisfy the requirements of 35 U.S.C. § 103(a). As such, these claims are allowable.

Rejection under 35 U.S.C. § 103 (a)

Claims 1-5 and 10-12 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Liu as applied to claim 1 above, and further in view of U.S. Patent No.: 5,874,301 to Keller, of record.

Applicants respectfully traverse.

The Examiner alleges that "Liu '535 obviates all of the limitations of the Applicant's claims." Applicant's have discussed the instant application as it relates to Liu '535 above, and for the sake of brevity, will not be repeated here as the Examiner raises the same issues on page 8 and 9 of the Office Action. With respect to the Examiner's allegation that "one of ordinary skill in the art at the time of the invention would have known that time is needed to allow differentiation of the cells and changes in gene expression," applicants submit the following. As discussed above, Liu '535 does not teach all of the limitations taught by applicants' claim 1 and claims that are dependent on claim 1 either directly or indirectly. Specifically, Liu '535 does not teach any time frame regarding the contacting of stem cells, especially embryonic stem cells, with a test substance. Furthermore, the examiner has admitted on page 9, 2nd paragraph of the Office Action that "**Liu '535 does not teach** these cell-type limitations..." (Emphasis added).

The Examiner further alleges that "Keller '301 specifically teaches that '[t]he cells are useful ... to identify compounds that control precursor cell growth and differentiation.

Therefore, one of ordinary skill in the art would have modified Liu '535 to provide a method of screening compounds for cell growth and differentiation utilizing the embryonic stem cells as limited in the claims." (Page 9, last paragraph of the Office Action). Applicants respectfully traverse.

The Examiner asserts that Keller teaches the isolation of stem cells; embryonic stem cells; mouse cells; preferred culture times (see 2nd paragraph, page 9 of the Office Action), to provide motivation for combining Liu '535 in view of Keller '301. However, Keller does not teach, either directly or indirectly the subject matter of the instant application. Example 1, cited by the Examiner, teaches the maintenance of an embryonic stem cell cell-line that was originally derived from a mouse strain. (See Keller '301, Example 1, col. 32, lines 30-31). Furthermore, col. 2, lines 5-8 directed to a cell-line that is "referred to as embryonic stem (ES) cells." Therefore, ES cells disclosed by Keller are embryonic stem cell-lines and not naïve, freshly isolated embryonic stem cells as disclosed and taught by applicants.

As provided in MPEP 2143.01, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F. 2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F. 2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). As provided above, the references cited, alone or in combination, include no such teaching, suggestion or motivation.

Furthermore, and as provided in MPEP 2143.02, a prior art reference can be combined or modified to reject claims as obvious as long as there is a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Additionally, it also has been held that if the proposed modification or combination would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. Further, and as provided in MPEP-2143, the teaching or suggestion to make the claimed combination and the reasonable suggestion of

success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As can be seen from the forgoing discussion regarding the disclosures of the cited references, there is no reasonable expectation of success provided in any reference. "...Before obviousness may be established, the Examiner must show that there is either a suggestion in the art to produce the claimed invention or a compelling motivation based on sound scientific principles." *Ex Parte Kranz*, 19 U.S.P.Q. 2d 1216, 1218 (BPAI 1990) (emphasis added). The Federal Circuit also has indicated that a prior art reference that gives only general guidance and is not all that specific as to particular forms of a claimed invention and how to achieve it, may make a certain approach obvious to try, but does not make the invention obvious. *Ex Parte Obukowicz*, 27 USPQ2d 1063, citing *In re O'Farrell*, 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988).

As the Federal circuit has stated, "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1783-84 (Fed. Cir. 1992). Obviousness may not be established using hindsight or in view of the teachings or suggestions of the inventor. *Para-Ordance Mfg. v. SGS Importers Int'l, Inc.*, 73 F.2d 1085, 1087, 37 USPQ2d 1237, 1239 (Fed. Cir. 1995).

It is respectfully submitted that for the foregoing reasons, claims 1-5 and 10-12 are patentable over the cited reference(s) and satisfy the requirements of 35 U.S.C. § 103 (a). As such, these claims are allowable.

Claims 1 and 6 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Liu '535 as applied to claim 1 above, and further in view of Thomson, et al. (1998) Science, 282: 1145-1147, of record.

Applicants respectfully traverse.

Applicants have discussed in detail above, as to why the instant invention is novel and patentable over Liu '535 and for the sake of brevity these arguments will not be repeated here. The Examiner alleges that one of ordinary skill in the art "would have been motivated to modify the teachings of Liu '535 by the use of human embryonic stem cells as taught in Thomson '98, because Thomson '98 teaches that such embryonic stem cells are useful for drug discovery (ABSTRACT)."

Thomson '98 discloses pluripotent cell lines (See ABSTRACT). Thomson teaches away from using embryonic stem cells as taught by applicants invention. Embryonic cells taught by applicants are totipotent stem cells which can differentiate into any cell lineage and are not limited to a specific cell lineage as are pluripotent stem cells. In addition, Thomson, as all the references cited by the Examiner teach the use of cell-lines and not the freshly isolated embryonic stem cells as taught by the instant invention. Therefore, the stem cell-lines allegedly disclosed by Thompson '98 are already committed to certain differentiation pathways and are immortalized cell lines. The deficiencies of Thomson cannot make up for the deficiencies of Liu and hindsight reconstruction of the applicants invention based on the applicants disclosure is simply improper.

It is respectfully submitted that for the foregoing reasons, claims 1-6 are patentable over the cited reference(s) and satisfy the requirements of 35 U.S.C. § 103 (a). As such, these claims are allowable.

Claims 1 and 20 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Liu, as applied to claim 1 above and further in view of U.S. Patent No. 5,143,854 to Pirrung of record.

Applicants respectfully traverse.

Applicants have discussed the novelty of applicants invention over Liu '535 above, and for the sake of brevity, these arguments will not be discussed here. The Examiner admits that "Liu '535 does not teach the aspect of utilizing gene chip technology in the screening for tissue-

specific gene expression." (See Office Action, page 13, 2nd paragraph. Emphasis added). Accordingly, Liu '535 fails to teach or disclose the applicants invention.

The Examiner alleges on page 13, 3rd paragraph of the Office Action that: "Pirrung '854 teaches the use of such gene chip technology for the analysis of arrays of peptides for activity (ABSTRACT). Specifically, Pirrung '854 teaches that such technology is useful for '[s]creening large numbers of polymers for biological activity,' (col. 3, lines 39-41)." Applicants respectfully traverse. Pirrung is specifically directed to screening of polypeptides and mentions polymers in general.

The Examiner further alleges that "both Liu '535 and Pirrung '854 have been shown successful, one would expected success with their combinations." (See page 14, first two lines of the Office Action). First, the Examiner does not provide any evidence how Liu '535 or Pirrung '854 have been successful. Second, assuming *arguendo*, such a success existed, such success begs the question as to why, Liu '535 does not teach or disclose gene chip technology since Pirrung '854 issued seven years prior to Liu's filing date, would not have been obvious to Liu? Accordingly, applicants submit that it was not even obvious to Lui '535 to incorporate any disclosure by Pirrung.

Thus, one of ordinary skill in the art still would have no expectation of success, as neither of these two references teach or suggest claim 1, the references, even if properly combinable, do not teach or suggest applicants claim 1 and those claims that depend on claim 1 either directly or indirectly. Especially so, since Pirrung provided neither the motivation nor reasonable expectation of success to Liu.

It is respectfully submitted that for the foregoing reasons, claims 1 and 20 are patentable over the cited reference(s) and satisfy the requirements of 35 U.S.C. § 103 (a). As such, these claims are allowable.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application

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with claims 1-6 and 8-20 is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with the Applicants' attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at telephone number shown below.

The Director for Patents is hereby authorized to charge any deficiency in fees due or credit an excess in fees with the filing of the papers submitted herein during prosecution of this application to Deposit Account No. 50-0951.

Date: 8-24-04

Respectfully submitted,
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